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Docket No.: PF-0678 US

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1652

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By: _____ Printed: Lisa McDill

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yue et al.

Title: ISOLATED POLYNUCLEOTIDE ENCODING A HUMAN PSST SUBUNIT OF THE NADH:UBIQUINONE OXIDOREDUCTASE COMPLEX (AS AMENDED)

Serial No.: 09/525,867 Filing Date: March 15, 2000

Examiner: Ramirez, D. Group Art Unit: 1652

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Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard; and
2. Reply Brief (12 pp., in triplicate).

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Respectfully submitted,

INCYTE CORPORATION

Date: February 17, 2004

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REPLY BRIEF ON APPEAL

Sir:

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated December 16, 2003 ("the Examiner's Answer") in the above-identified application. This Reply Brief on Appeal is timely filed Tuesday, February 17, 2003, as Monday, February 16, 2003 is a holiday.

In the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of Claim 31 under 35 U.S.C. § 112, first paragraph for alleged lack of written description of the claimed variant polynucleotides; and

(4) maintained the rejection of Claim 31 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement of the claimed variant polynucleotides.

I. Written Description Rejection

Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the Specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Appellants were in possession of the claimed polynucleotide comprising a naturally occurring

polynucleotide sequence having at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9.

The Examiner alleged that "the genus claimed is not adequately described since it almost certainly encompasses polynucleotides encoding polypeptides of variable function which are not disclosed by the specification." (Examiner's Answer, page 11.)

The Examiner discounts the claim limitations of "at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9" and attempts to introduce a limitation of "function" to the polynucleotide variants, a limitation which is not present in the pending claims. The Examiner discounts the limitation that the claimed polynucleotides comprise a naturally occurring polynucleotide sequence.

The Examiner's position is clearly contrary to the USPTO's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described** in the specification, then the adequate description requirement is met. (citations omitted, emphasis added)

Here, there simply is no requirement that the claims recite particular variant polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polynucleotide variants are defined in terms of SEQ ID NO:9 ("An isolated polynucleotide selected from the group consisting of . . . b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9.").

The Examiner alleges that "there is no means for a skilled artisan to know which of the enormous number of polynucleotides having at least 80% sequence identity to the polynucleotide of SEQ ID NO:9 are within the naturally occurring genus claimed." (Examiner's Answer, page 11.) Appellants note that sequence information is not provided in a vacuum. Identification of

the source of the sequence will typically allow one to determine if it is naturally-occurring. Also, attempted deceit to hide the source will not preclude infringement.

Because the recited polynucleotide variants are defined in terms of SEQ ID NO:9, the precise chemical structure of every polynucleotide fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

II. Enablement Rejection

The Examiner rejected Claim 31 under 35 U.S.C. §112, first paragraph, alleging that the "specification, while enabling for the polynucleotide of SEQ ID NO:9, does not reasonably provide enablement for (1) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9, (2) a polynucleotide completely complementary to the polynucleotide of (1), or (3) an RNA equivalent of (1) or (2). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." (Examiner's Answer, pages 6-7.)[1]

The Examiner did not consider the Bedilion Declaration and attached exhibits, alleging that "the declaration, which was submitted in response to the Final Action, was not necessitated by new issues raised by the Examiner such that it would have been proper under 37 CFR 1.195." (Examiner's Answer, page 29.) Appellants note the Examiner's allegations, but do not agree.

Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have been able to make and use the claimed polynucleotide variants, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art."

A. How to make

SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 1 and 6-7 of the Sequence Listing). Variants of SEQ ID NO:1 and SEQ ID NO:9 are disclosed, for example, on page 18, line 28 through page 19, line 15, page 20, lines 29-32,

[1] Appellants note that the enablement rejection as listed in the Office Action mailed March 12, 2002, in the Final Office Action mailed February 24, 2003, and in the Advisory Action mailed June 23, 2003 did not appear to state that the claimed complementary sequences or RNA equivalents were not enabled.

and page 21, lines 4-12. Incyte clones in which the nucleic acids encoding the human MITP-1 were first identified and libraries from which those clones were isolated are disclosed, for example, in Tables 1, 3, and 4. Chemical and structural features of MITP-1 are disclosed, for example, in Table 2. "Naturally occurring" polynucleotide sequences occur in nature; they are not created exclusively in a laboratory. The Specification discloses how to find naturally occurring analogs and homologs in other individuals and species (e.g., page 39, lines 3-6) and how to use CLUSTAL V and BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9" scope (e.g., page 11, line 22 through page 12, line 32). The making of the claimed polynucleotides by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 17, lines 16-19, page 21, lines 31-35, page 23, lines 21-25, page 24, lines 14-16, and page 34, lines 24-31. This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner states that "the specification fails to teach how to isolate and/or identify naturally-occurring polynucleotides as claimed, such as allelic variants of the polynucleotide sequence of SEQ ID NO:9, encoding PSST subunits of the NADH:ubiquinone oxidoreductase complex." (Examiner's Answer, page 28.) Appellants refer the Board to the text of Claim 31. Claim 31 does not limit the polynucleotide variants to those "wherein said polynucleotides encode PSST subunits of the NADH:ubiquinone oxidoreductase complex." As discussed supra the Specification adequately enables the making of the claimed polynucleotides. And indeed, the Examiner acknowledges that "making the claimed polynucleotides is not undue experimentation since synthesis of polynucleotides is known in the art." (Examiner's Answer, pages 27-28.)

B. How to Use

1. Overview

In the rejection of the claimed invention for alleged lack of enablement, the Examiner does not disprove the following:

1) that the claimed polynucleotide variants are expressed in humans; and

2) that all, or almost all, polynucleotides expressed in humans have specific and substantial uses for measuring undesired side effects of drug candidates in toxicological testing.

It follows that the claimed invention is, by more than a reasonable probability, useful. There is no dispute that the Appellants need show no more than a reasonable probability that the claimed invention is useful to meet the requirements of 35 U.S.C. § 112, first paragraph.

The Examiner however continues to insist that the Appellants prove not only reasonable probability of usefulness, but also the "specific diseases, conditions, and/or biological processes which are related to the expression of such polynucleotide." (Examiner's Answer, page 31.)

In this case, Appellants have identified the claimed polynucleotides and the polypeptides encoded by the claimed polynucleotides by association in defined and narrow groups: the families of expressed polynucleotides and expressed polypeptides. As demonstrated below and in the Appeal Brief filed July 28, 2003, because members of the families of expressed polynucleotides and expressed polypeptides are predominantly useful, Appellants can state with great confidence that the claimed invention is useful. How the invention actually works and "specific diseases, conditions, and/or biological processes which are related to the expression of such polynucleotide" are utterly irrelevant to the analysis.

2. Responses to Specific Arguments by Examiner

The Examiner bases the enablement rejection on two issues, that the uses of the claimed polynucleotides in toxicology testing "are not specific to the claimed genus of polynucleotides" and that "the results of gene expression assays would be meaningless without further experimentation." (Examiner's Answer, pages 34 and 35.) Appellants demonstrate below that the claimed uses meet the requirement that the claimed invention yield a "specific benefit" and why these uses would not require "further experimentation.

a. Irrelevance of differential expression or disease association to use in toxicology testing

The Examiner alleges that uses in toxicology testing "are enabled for a specific polynucleotide only when one of skill in the art is provided with some knowledge or guidance as to the specific diseases, conditions, and/or biological processes which are related to the expression of such polynucleotide" and "[s]ince the specification does not disclose a correlation between any disease or disorder and an altered level of expression or a mutated form of the claimed polynucleotides, the results of gene expression assays would be meaningless without further research." (Examiner's Answer, page 31.)

Appellants have demonstrated a use for the claimed polynucleotides irrespective of whether or not a person would wish to perform additional experimentation on biological function or associated "biological processes" as another use. The fact that additional experimentation could be performed to determine the functionality of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides does not preclude, and is in fact irrelevant to, the actual use of the invention. That use exists today regardless of the specific function of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The Examiner confuses use with function.

Appellants need not demonstrate whether the claimed polynucleotides, or the polypeptides encoded by the claimed polynucleotides, are differentially expressed or associated with any disease, only whether the claimed polynucleotides or their encoded polypeptides are useful. The claimed polynucleotides and the polypeptides encoded by the claimed polynucleotides are useful whether or not the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are differentially expressed or associated with any disease.

The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides can be used for toxicology testing in drug discovery without any knowledge of differential expression or disease association of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. Monitoring the expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide or polypeptide, regardless of the differential expression or disease association of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to other polynucleotides or polypeptides regardless of any possible use for measuring the properties of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides.

Appellants note that monitoring the expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polynucleotide or polypeptide is affected in any way by exposure to a test compound, and if that particular polypeptide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may

have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology testing using cDNA microarrays reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from a cDNA microarray in a protein expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide or polypeptide whose expression is being monitored.

As an example, any actin gene or histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. An actin gene or histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed actin gene or histone gene is surely an excellent subject for toxicology studies when developing drugs targeted to other genes. A drug candidate which alters expression of an actin gene or histone gene is toxic because disruption of such a constitutively expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of an actin gene or histone gene is a good measure of the toxicity of that candidate, particularly in in vitro cellular assays at an early stage of drug development. The use of any particular human-expressed actin gene or histone gene in toxicology testing is specific and substantial because a toxicology test using that actin gene or histone gene cannot be replaced by a toxicology test using a different gene, including any other actin gene or histone gene. This specific and substantial use requires no knowledge of the biological function or disease association of the actin gene or histone gene.

b. Use of all expressed polynucleotides in toxicology testing

The Examiner discounts the use of the claimed polynucleotides in gene expression monitoring assays, stating that "[t]hese uses are applicable to <u>any</u> polynucleotide and are not specific to the claimed genus of polynucleotides." (Examiner's Answer, page 34, emphasis in original.) The Examiner doesn't point to any law, however, that says a use that is shared by a large class is somehow not a use. If all of the class of expressed polynucleotides can be so used, then they all are enabled. The issue is, once again, whether the use of the claimed polynucleotides and encoded polypeptides is enabled, not whether other compounds may be similarly used. Nothing in the law says that an invention must have a "unique" use. Indeed, the whole notion of "well-established" uses PRESUPPOSES that many different inventions can have

the exact same use (if the Examiner's argument were correct, there could never be a well-established use, because you could always find a generic group with the same use!).

Appellants note that to meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966).

Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility or enablement on the grounds that it is not "particular" or "unique" to the specific invention.

c. Use of claimed complementary sequences and ribonucleotide equivalents

The claimed polynucleotide variants, complementary sequences, and ribonucleotide equivalents comprise products of expressed genes or encode polypeptides comprising expressed polypeptide sequences. Therefore, these polynucleotides are useful in toxicology testing as described above.

In addition, the Specification discloses the use of the claimed complementary polynucleotides and RNA equivalents on, e.g., page 8, lines 16-26, page 33, lines 16-23, page 34, lines 1-11, page 38, lines 25-30, page 40, line 35 through page 41, line 6, and page 49, lines 3-11.

d. Irrelevance of "function"

The Examiner alleges that the "specification fails to disclose (1) other functions for all polynucleotides comprising a naturally occurring sequence 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9," that "structural homologs may not share a similar function," and that therefore the claimed polynucleotide variants are not enabled. (Examiner's Answer, pages 7 and 8, emphasis in original.) However, "function" is irrelevant to the use of the recited polynucleotide variants, e.g., in toxicology testing (see for example, Specification, page 38, line 25 through page 41, line 24).

e. The Examiner's reliance on *Brenner v. Manson* is misplaced

This is not a case in which biological function or disease association or differential expression is necessary to provide a link between the claimed invention on one hand, and a

compound of known use on the other. Given that the claimed invention is disclosed in the priority Yue '655 application to be useful as a tool in a number of gene expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function or disease association or differential expression of the claimed polynucleotides or the encoded polypeptides is superfluous information for the purposes of establishing enablement.

The fact that the claimed invention already has a disclosed use as a tool in then available technology (such as cDNA microarrays) distinguishes it from those few claimed inventions found not to have a use. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases, *Brenner v. M*anson, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect. (Examiner's Answer, e.g., pages 39 and 51.)

Brenner concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the claimed polynucleotides comprise expressed polynucleotide sequences that were disclosed to be useful in the priority Yue '655 application for many known applications involving gene expression monitoring analysis. Their use is not a matter of guesswork. They are not random DNA or protein sequences that might or might not be useful as a scientific tool. Unlike the steroid in *Brenner*, the use of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions.

And, the uses disclosed in the application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug.

Accordingly, in this case, biological function or disease association or differential expression is in fact superfluous information for the purposes of demonstrating enablement. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function, as the evidence presented by the Appellants demonstrates. Given that the claimed invention has disclosed and well-established uses, the Appellants need not demonstrate a use by imputation or by showing disease association or differential expression.

In the end, the Examiner has failed to recognize that new technologies, such as those involving the use of cDNA microarrays to conduct gene expression analyses, have made useful biological molecules that might not otherwise have been useful in the past. See *Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polynucleotide or protein could be usefully employed without further research. It has created a need for new tools, such as the claimed polynucleotides, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and real-world benefits to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

C. Summary

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any reasons why one would doubt that the guidance provided by the present Specification would enable one to make and use the claimed polynucleotide variants, complementary sequences, and ribonucleotide equivalents. Hence, a prima facie case for non-enablement has not been established with respect to the recited polynucleotides.

CONCLUSION

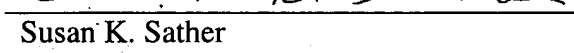
For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,
INCYTE CORPORATION

Date: February 17, 2004



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